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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/006,972 | 12/04/2001 | Kenneth W. Dobie | RTS-0335 | 2850 |

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| EXAMINER | |
|---|---|
| EPPS FORD, JANET L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/006,972 | DOBIE, KENNETH W. | |
| | Examiner | Art Unit | |
| | Janet L. Epps-Ford, Ph.D. | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-10,12-14 and 19-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10,12-14 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Arguments*

1. Applicant's arguments with respect to claims 1-2, 4-14 and 19-20 have been considered but are moot in view of the new ground(s) of rejection.

### *Claim Rejections - 35 USC § 102*

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1-2, and 19-20 are rejected under 35 U.S.C. 102(a or e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sims et al. (WO200174295 A2).

Sims et al. (WO200174295 A2) disclose an oligonucleotide (huPLSCR3; see page 55, example #7) of 22 nucleotides in length that is antisense to nucleotides 1259-1280 of SEQ ID NO: 3 of the instant application. However, Sims et al. do not specifically teach that the disclosed oligonucleotide functions to inhibit the expression of phospholipid scramblase 3 expression.

Absent evidence to the contrary, since the oligonucleotide of Sims et al. meet all the structural limitations of the instant claims, one of skill in the art at the time the instant invention was made would have expected that the oligonucleotide of Sims et al. would inherently function to inhibit the expression of phospholipid scramblase 3 since it meets all the structural characteristics of the claimed compounds.

See MPEP § 2112[R-2]III, which states "[W]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims."

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-2, and 19-21 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Landers et al. (WO200018960 A2).

Landers et al. (WO200018960 A2) disclose an oligonucleotide of 17 nucleotides in length that comprises an 11 nucleobase portion of SEQ ID NO: 59 of the instant application. SEQ ID NO: 59 is an antisense compound targeted to nucleobases 1034 through 1635 of SEQ ID NO: 3 of the instant application, see Table 1. However, Landers et al. do not specifically teach that the disclosed oligonucleotide functions to inhibit the expression of phospholipid scramblase 3 expression.

Absent evidence to the contrary, since the oligonucleotide of Landers et al. meet all the structural limitations of the instant claims, one of skill in the art at the time the instant invention was made would have expected that the oligonucleotide of Landers et al. would inherently function to inhibit the expression of phospholipid scramblase 3 since it meets all the structural characteristics of the claimed compounds.

See MPEP § 2112[R-2] III, which states "[W]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims."

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2, and 4-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter).

Applicants have amended the instant claims to recite the following A compound 8 to 50 nucleobases in length targeted to nucleobases 1034 through 1635 of a 3'-untranlsated region of a nucleic acid molecule encoding human phospholipid scramblase 3 (SEQ ID NO: 3), wherein said compound specifically hybridizes with said nucleic acid molecule encoding phospholipid scramblase 3 and inhibits the expression of phospholipid scramblase 3. The current amendment to the claim to add the nucleobase range of 1034 through 1635 does not find support in the specification as filed. For example, the claim requires that the compound targeted to nucleobases 1034 through 1635 inhibit the expression of phospholipid scramblase 3, however compounds targeted to nucleobases 1351-1370, 1359-1378 and 1362-184, all of which target between nucleobases 1034 through 1635, show 0% inhibition of phospholipid scramblase 3 expression. Additionally, the specification as filed does not provide support for designing compounds which target all nucleobases between 1034 through 1635, for example, the specification does not provide support for targeting nucleobases 1087 through 1186 of SEQ ID NO: 3 of the instant specification.

Applicants are not permitted to add new matter to an application after its filing date. See MPEP § 608.04(b). Applicants must cancel the new matter recited in the instant claims in response to this Office Action.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 22-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 recites "the compound of claim 22." There is lack of antecedent basis for this limitation. Claim 22 does not further limit a previous claim since it depends from itself. Claim 23 is also rejected since the invention set forth in claim 22 is indefinite, and the limitations set forth in claim 23 do not correct this deficiency.

***Claim Rejections - 35 USC § 103***

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-2, 4-14 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmer and Sims (WO 97/37225 and WO 99/1935), Sims et al. (WO 99/36536), in view of Wiedmer et al. (2000), Sims et al. (WO200174295 A2), Branch (1998) Monia et al. and Agrawal et al.

12. Disclosed in the PCT publications WO 97/37225 and WO 99/19352 are a preparation of a phospholipid scramblase, a recombinant DNA sequence encoding a phospholipid scramblase protein and expression vectors used to express the protein (see for example page 15 of WO 97/37225). Also disclosed are inhibitors of phospholipid scramblase including monoclonal

antibodies, and generally disclosed are antisense nucleotides derived from a DNA sequence encoding a phospholipid scramblase (see page 20 of 97/37225), as well as peptides and peptidomimetics. Further disclosed are methods to treat various diseases and/or conditions using said inhibitors, methods to quantitate the amount of phospholipid scramblase present, cells genetically engineered not to express phospholipid scramblase and those wherein the phospholipid scramblase promoter is altered to increase or decrease the expression of the gene (Wiedmer and Sims, 1999; Wiedmer and Sims, 1997).

Disclosed in the PCT publication WO 99/36536 are methods to extend the viability of mammalian cells by inhibiting the expression of a phospholipid scramblase, wherein the inhibition is via a phospholipid scramblase antisense RNA molecule, a mutant or truncated form of a phospholipid scramblase such as an alternatively spliced phospholipid scramblase mRNA, a scramblase containing non-conservative substitutions, and by preventing posttranslational modifications such as fatty acylation. Also disclosed are methods to decrease the viability of metastatic or cancer cells by increasing the expression of phospholipid scramblase. Methods for diagnosing cancer are also disclosed, wherein said method comprises determination of the levels of phospholipid scramblase in human patients (see page 73, claim 5 of Sims et al., 1999).

13. However, none of the above references disclose antisense compounds of 8 to 0 nucleobases in length targeting scramblase 3, or wherein said antisense oligonucleotides comprise the various modifications recited in the instant claims.

14. Phospholipid scramblase 3 (also known as PLSCR3, HuPLSCR3 and MuPLSCR3) was isolated as one of three new members of the phospholipid scramblase gene family (Wiedmer et al., Biochim. Biophys. Acta, 2000, 1467, 244-253). Upon identification of sequences in the EST

database potentially encoding these three new phospholipid scramblase family members, a full-length cDNA encoding phospholipid scramblase 3 was obtained by PCR from a human erythroleukemia cell (HEL) cDNA library (Wiedmer et al., Biochim. Biophys. Acta, 2000, 1467, 244-253). This sequence corresponds to the phospholipid scramblase 3 sequence according to SEQ ID NO: 3 of the instant application.

15. Sims et al. (WO200174295 A2) disclose an oligonucleotide (huPLSCR3; see page 55, example #7) of 22 nucleotides in length that is antisense to nucleotides 1259-1280 of SEQ ID NO: 3 of the instant application.

16. Branch teach that in order to maximize target site specificity the length of antisense oligonucleotides should be 17 base pairs or longer, since sequences of 17 base pairs or more would have a high probability of occurring only once in the haploid human genome. However, increasing the length of the oligonucleotide beyond this minimum would likely stabilize non-specific binding to mismatch sequences (p. 47, para. 5-6).

17. Monia et al. (6,114,517) teach the design of antisense oligonucleotides comprising various modifications, including phosphorothioate modified internucleoside linkages (col. 8, line 41-43), 2'-O-methoxyethyl sugar modifications (col. 10, line5), 5-methylcytosine modified nucleobase (col. 10, line 31-32), and wherein the antisense oligonucleotide is a chimeric oligonucleotide (col. 11, line 51). The modified or substituted oligonucleotides of Monia et al. are preferred over native (unmodified or unsubstituted) forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced binding to target and increased stability in the presence of nucleases (col. 8, lines 2-6). Additionally, Monia et al. teach the use compositions comprising antisense oligonucleotides and a pharmaceutically acceptable carrier or

diluent, and further comprising a colloidal dispersion system in order to enhance the stability of oligonucleotides introduced into cells and to target oligonucleotides to a particular tissue or cell (col. 15, lines 19-41).

18. Agrawal provides motivation for designing antisense oligonucleotides targeting various regions of a target mRNA, including for example the coding region and the 5'-UTR and 3'-UTR of a target mRNA. According to Agrawal et al. "[I]t is considered preferable, therefore, to screen a number of oligonucleotides that encompass different regions on RNA to identify a set of optimal target sites, including the 5'- and 3'-untranslated regions (UTRs), initiation codon site, coding region and intron-exon junctions." (page 77, 1st para.) Additionally, Agrawal et al. generally states (regarding the feasibility of utilizing antisense technology), "antisense technology has become an essential laboratory tool to study and understand the function of any newly discovered genes in recent years."

19. It would have been obvious to one of ordinary skill in the art at the time of filing to modify the teachings of Wiedmer and Sims (WO 97/37225 and WO 99/1935), Sims et al. (WO 99/36536), in view of Wiedmer et al. (2000), Sims et al. (WO200174295 A2), Branch (1998) Monia et al. and Agrawal et al. to produce the compounds and compositions according to the present invention. One of ordinary skill in the art would have been motivated to modify the teachings of Wiedmer and Sims (WO 97/37225 and WO 99/1935), and Sims et al. (WO 99/36536), in view of Wiedmer et al. (2000), Sims (2001), Branch (1998), Monia et al. and Agrawal et al. to make the antisense compounds targeting phospholipid scramblase 3 according to the present invention. One of ordinary skill in the art would have been motivated to design antisense compounds to comprise about 17 nucleobases in length or more, because antisense

compounds of about 17 nucleobases in length would enhance target site specificity for the antisense to its target mRNA (Branch). One of ordinary skill in the art would have been motivated to utilize the oligonucleotide disclosed by Sims et al. (2001) as an antisense oligonucleotide directed against phospholipid scramblase 3 mRNA, since this oligonucleotide is disclosed in the prior art as having a structure that is antisense to the phospholipid scramblase 3 cDNA sequence. One of ordinary skill in the art would have been motivated to further modify the antisense compounds of Wiedmer and Sims, and Sims et al. (97, 99, 2001) to comprise phosphorothioate modified internucleoside linkages, 2'-O-methoxyethyl sugar modifications, 5-methylcytosine modified nucleobases, or wherein said antisense compound is a chimeric compound, because according to Monia et al. these modifications would enhance the cellular properties of antisense compounds as compared to unmodified antisense compounds. Moreover, one of ordinary skill in the art would have been motivated to design compositions comprising the antisense compounds according to the present invention and a pharmaceutical carrier or diluent, and further comprising a colloidal dispersion system because Monia et al. teach that compositions designed according to this manner would enhance the stability of oligonucleotides introduced into cells and would help to target oligonucleotides to a particular tissue or cell.

20. Moreover, one of ordinary skill in the art seeking methods to extend the viability of mammalian cells by would have been motivated to design antisense oligonucleotides targeting phospholipid scramblase 3, since Sims et al. (1999) teach that inhibiting the expression of a phospholipid scramblase in mammalian cells increases the viability of these cells. Moreover, one of ordinary skill in the art seeking to further understand the role of phospholipid scramblase 3 in mammalian cells would have been motivated to design antisense oligonucleotides targeting the

mRNA encoding the phospholipid scramblase 3 gene, since according to Agrawal, if the sequence of a gene is known, designing antisense oligonucleotides to target that gene would allow the ordinary skilled artisan to further explore and understand the function of that particular gene.

21. Therefore, the invention as a whole is prima facie obvious over Wiedmer and Sims (WO 97/37225 and WO 99/1935), and Sims et al. (WO 99/36536), in view of Wiedmer et al. (2000), Sims et al. (2001) Branch (1998), Monia et al. and Agrawal et al.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Patent Examiner
Art Unit 1635

*JLE*